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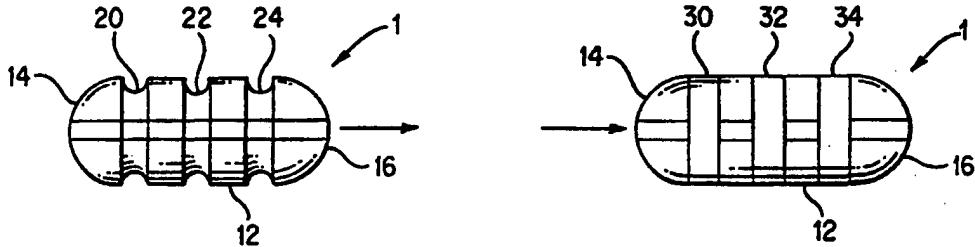
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/20		A1	(11) International Publication Number: WO 99/56730
			(43) International Publication Date: 11 November 1999 (11.11.99)
(21) International Application Number: PCT/US99/09575		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 3 May 1999 (03.05.99)			
(30) Priority Data: 60/084,646 7 May 1998 (07.05.98) US 09/274,648 23 March 1999 (23.03.99) US			
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(54) Title: METHOD OF FABRICATING A BANDED PROLONGED RELEASE ACTIVE AGENT DOSAGE FORM



(57) Abstract

The present invention is directed to an active agent dosage form and methods of its fabrication which is useful for the prolonged delivery of an active agent formulation to a fluid environment of use. The active agent dosage form is a matrix that has on its surface one or more insoluble bands located in complementary grooves. The invention is also directed to articles of manufacture, methods and systems for fabricating the active agent dosage form.

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1 METHOD OF FABRICATING A BANDED PROLONGED RELEASE
2 ACTIVE AGENT DOSAGE FORM

3
4 FIELD OF THE INVENTION

5
6 The present invention is related to the prolonged delivery of an active
7 agent. More particularly, it is directed to an improved method of making a
8 banded active agent dosage form which is useful for delivering a beneficial
9 agent to a fluid environment of use.

10
11 BACKGROUND OF THE INVENTION
12

13 Tablets, capsules, caplets and many other types of devices have been
14 used for dispensing a beneficial agent to a fluid environment of use. Easy
15 manufacture of a device that provides for prolonged delivery of an active
16 agent in a controlled and predictable manner continues to be a goal,
17 especially in the area of drug delivery.

18
19 U.S. Patent No. 4,290,426 to Luschen et al describes a cylindrical
20 dispenser for releasing a beneficial agent into a fluid environment at a rate
21 that is governed by the fluid-induced relaxation of a polymeric agent
22 contained within the dispenser. The cylindrical dispenser includes an
23 impermeable container that has within it a reservoir and a passageway from
24 the reservoir to the exterior of the container. The reservoir contains a
25 polymer and a beneficial agent. The polymer imbibes fluid from the
26 environment and thereby undergoes relaxation, releasing the beneficial agent

1 from the device. The amount of agent released is dependent on the rate of
2 relaxation of the polymer over time.

3

4 Coated dosage forms have also been suggested for delivery of a
5 controlled amount of a beneficial agent over a prolonged period of time. U.S.
6 Patent No. 5,256,440 describes a process for producing a film coated dosage
7 form. A continuous groove is inscribed in a dosage form core. A latex film is
8 coated onto the core, the groove defining a fixed zone and a detachable zone
9 for the film. The detachable portion of the latex film detaches when it is
10 exposed to the environment of use, thereby exposing a discrete portion of the
11 dosage form core surface. The remainder of the film remains attached to the
12 dosage form core. The exposed portion of the dosage form surface erodes
13 and releases active agent to the environment of use.

14

15 Coated tablets for constant and prolonged drug release are described
16 by Conte et al in J. Controlled Release, Vol. 26, (1993) pages 39-47. These
17 GEOMATRIX™ Systems are swellable matrices that are coated or tabletted
18 with polymeric barrier layers. Release performances of the systems are
19 modulated as a result of the restriction of the releasing surface by the
20 polymeric barrier layer coatings. As the extent of coating of the system's
21 surface is increased, the release kinetics of the system shift toward constant
22 release. These systems are further described in U.S. Patent No. 4,839,177 to
23 Colombo et al.

24

25 U.S. Patent No. 5,534,263 describes a banded dosage form which is
26 useful for the sustained delivery of an active agent formulation to a fluid
27 environment of use. The active agent dosage form is a matrix that has on its
28 surface two or more insoluble bands. The dosage form described provides
29 significant advantages over other prior art devices for the sustained delivery
30 of an active agent.

31

SUMMARY OF THE INVENTION

2

3 It has been observed that banded devices such as those described in
4 U.S. Patent No. 5,534,263 ('263 patent), which is incorporated herein by
5 reference in its entirety, have significant advantages for prolonged delivery of
6 an active agent formulation to a fluid environment of use. It has now been
7 discovered that if the active agent formulation matrix is provided with at least
8 one groove, prior to the banding process described in the '263 patent, the
9 groove can be used as a register to orient the dosage form during the
10 banding process. Additionally, the groove allows for more uniform deposition
11 of the banding material. In that manner, improved dosage forms are provided
12 and savings and manufacturing advantages are achieved.

13

14 Accordingly, the present invention is directed to an improved method
15 and system for manufacturing banded dispensing devices, to improved
16 articles of manufacture, and to components that facilitate manufacture of the
17 devices.

18

19 In one aspect, the invention comprises an active agent dosage form for
20 the prolonged delivery of an active agent formulation to a fluid environment of
21 use, the dosage form comprising an active agent formulation matrix having at
22 least one groove circumscribing a portion of the surface thereof and an
23 insoluble band positioned in the groove.

24

25 In another aspect the invention comprises a blank for formation of an
26 active agent dosage form for controlled delivery of an active agent, the blank
27 comprising an active agent formulation matrix having at least one groove
28 circumscribing a portion of the surface thereof.

29

1 In a further aspect the invention comprises a banding system for
2 fabricating an active agent dosage form comprising means for orienting a
3 blank having a groove and means for forming a band in the groove.

4

5 The invention comprises the following characteristics and features,
6 either alone or in combination with one or more of each other.

7

8 An active agent dosage form for the prolonged delivery of an active
9 agent formulation to a fluid environment of use, the dosage form comprising
10 an active agent formulation matrix having at least one groove circumscribing
11 a portion of the surface thereof and an insoluble band located in the groove;
12 the dosage form wherein the groove has the shape of a notch; the dosage
13 form wherein the groove has a continuous concave shape; the dosage form
14 wherein the depth of the groove is between 0.1 and 3 mm; the dosage form
15 wherein the width of the groove is between 0.5 and 10 mm; the dosage form-
16 wherein the outer surface and bands are coated to form a smooth, exterior
17 surface; and the dosage form having more than one groove circumscribing a
18 portion of the surface thereof and an insoluble band located in each groove.

19

20 A blank for formation of a pharmaceutical dosage form for controlled
21 delivery of an active agent, the blank comprising an active agent formulation
22 matrix having at least one groove circumscribing a portion of the surface
23 thereof; the blank wherein the groove has the shape of a notch; the blank
24 wherein the groove has a continuous concave shape; the blank wherein the
25 depth of the groove is between 0.1 and 3 mm; the blank wherein the width of
26 the groove is between 0.5 and 10 mm; the blank wherein the groove functions
27 as a location register; the blank wherein the groove is adapted to cooperate
28 with a printing means; the blank wherein the groove is adapted to cooperate
29 with a printing means having a latex source; and the blank wherein the
30 groove is adapted to cooperate with a printing means having a latex source
31 selected from acrylate esters.

1 A system for fabricating the dosage form from a blank comprising an
2 active agent formulation matrix and at least one groove on the surface
3 thereof, the system comprising means for orienting the blank by means of a
4 groove in the blank, and means for forming a band in a groove; the system
5 including means for transporting the blank; the system wherein the means for
6 orienting the blank includes means registering with one or more of the
7 grooves on the blank; the system wherein the means for orienting the blank
8 includes a rotatable wheel; the system wherein the band forming material
9 comprises a latex of acrylate polymers; the system wherein the acrylate
10 polymers comprise copolymers of ethylacrylate and methylmethacrylate; and
11 the system wherein the means for forming a band in a groove comprises
12 printing means.

13

14 A method of preparing an active agent dosage form for the prolonged
15 delivery of an active agent formulation to a fluid environment of use, the
16 dosage form comprising an active agent formulation matrix having at least
17 one groove circumscribing a portion of the surface thereof and a band of
18 insoluble material positioned in the groove, the method comprising forming a
19 blank having a groove corresponding to a desired location of the insoluble
20 band, and coating the groove with the insoluble material.

21

DESCRIPTION OF THE DRAWINGS

23

24 The figures are not drawn to scale, but are set forth to illustrate various
25 embodiments of the invention. Like numbers refer to like structures.

26

27 FIG. 1 is a side elevational view of one embodiment of a blank useful
28 for fabrication of the delivery device of the present invention, the blank being
29 in prepared form prior to printing of bands in the grooves on the surface of the
30 blank.

31

1 FIG. 2 illustrates the blank of FIG. 1 after the banding operation has
2 been completed.

3
4 FIG. 3 is a side elevational view illustrating a particular embodiment of
5 the blank of this invention having a groove formed as a concave surface.

6
7 FIG. 4 illustrates the blank of FIG. 3 after the banding operation has
8 been completed.

9
10 FIG. 5 is a side elevational view illustrating another embodiment of a
11 blank of this invention having a groove formed as a notch.

12
13 FIG. 6 illustrates the blank of FIG. 5 after the banding operation has
14 been completed.

15
16 FIG. 7 is a side, elevational view schematically illustrating the major
17 components of the banding system of the present invention.

18
19 FIG. 8 is a top view of the banding system illustrated in FIG. 7, the
20 tablet drying means not being shown.

21
22 FIG. 9 is an illustration of one embodiment of the printing station in the
23 banding means of the invention with a printing wheel having a substantially
24 planar printing surface.

25
26 FIG. 10 is an illustration of an alternate embodiment of the printing
27 station in the banding means of the invention with a printing wheel having a
28 concave printing surface.

29
30 FIG. 11 is a perspective view of a typical blank of this invention formed
31 from horizontal compression in a tabletting press.

1 DETAILED DESCRIPTION OF THE INVENTION
23 The present invention provides a delivery device and articles of
4 manufacture and systems and methods for fabrication of the device, the
5 device being useful for the prolonged delivery of an active agent formulation
6 to a fluid environment of use.

7

8 DEFINITIONS
910 The phrase "prolonged delivery" intends a period of delivery that lasts
11 for several hours to about 24 hours, usually up to about 20 hours, and often
12 between about 3 and 16 hours.

13

14 By "insoluble" is intended a material that will not dissolve, degrade or
15 erode in the environment of use during the delivery period.

16

17 By "apply" or "applied" or "application" is intended the deposition of
18 insoluble material, in liquid or in molten form, onto the active agent
19 formulation matrix. A variety of techniques may be used to apply the
20 insoluble material, including but not limited to Gravure-type printing, extrusion
21 coating, screen coating, brush coating, spraying, painting, and the Capsealer
22 process developed by TAIT Design & Machine Co., Manheim, PA and the
23 system developed and sold by Shionogi Qualicaps of Indianapolis, Indiana,
24 commonly referred to as the Quali-seal™ process. These systems can be
25 used with modification of their usual capsule feed systems to accommodate
26 the compressed tablet blanks typically used in the present invention.

27

28 The term "active agent formulation" intends the active agent or drug
29 optionally in combination with pharmaceutically acceptable carriers and
30 additional inert ingredients.

31

1 The term "active agent formulation matrix", as used herein, comprises
2 the active agent formulation in combination with a hydrophilic polymeric
3 material.

4

5 The "active agent dosage form" intends the active agent formulation
6 matrix as defined above with one or more bands of an insoluble material
7 applied onto its surface.

8

9 The term "blank" means an active agent formulation matrix formed
10 without any band but with at least one groove circumscribing a portion of its
11 surface. A blank may have more than one groove to facilitate placement of a
12 plurality of bands contemplated herein.

13

14 As used herein, the terms "therapeutically effective" amount or rate
15 refer to the amount or rate of the active agent needed to effect the desired
16 pharmacologic, often beneficial, result.

17

18 The dispensing devices of the invention embody improvements over
19 the dispensing devices described in U.S. Patent 5,534,263 ("263 patent"),
20 which is incorporated herein by reference. The dispensing devices of the
21 invention find use, for example, in humans or other animals. The
22 environment of use is a fluid environment and can comprise the stomach, the
23 intestinal tract, or a body cavity such as the peritoneum or vagina. A single
24 dispensing device or several dispensing devices can be administered to a
25 subject during a therapeutic program.

26

27 The dispensing devices of the invention are fabricated by methods and
28 with systems improved over that described in the '263 patent and the prior art.
29 In prior methods, the dispensing devices were produced from cylindrical
30 tablets having a uniformly continuous external surface without any grooves.
31 In the banding equipment unbanded tablets were rotated at a printing station

1 as banding material was applied to the external surface of the unbanded
2 tablets. Bands were thus applied to the external surface and the band
3 thickness resulted in a finished banded device having a non-uniform external
4 surface as can be seen from the illustrations in the figures of the '263 patent.
5 The unbanded tablets were rotated independently of the printing means and
6 had the tendency to wobble as the bands were applied. This resulted in some
7 of the bands being applied in a non-uniform manner, particularly around the
8 edges, and with non-uniform band thickness. Such non-uniformity may affect
9 the delivery profile of the active agent from the dispensing device and, as
10 such, a less than optimal delivery device is produced.

11

12 It has now been discovered that if an indexing or register means is
13 provided on the unbanded device prior to the banding operation, the banding
14 means can be configured to cooperate with the indexing or register means to
15 locate the unbanded device accurately at the location at which the insoluble
16 band material is placed on the unbanded device during the banding
17 operation. The indexing or register means may be provided by one or more
18 grooves, formed on a portion of the external surface of the unbanded device,
19 that cooperate with the banding means. Accordingly, bands can be applied
20 with greater uniformity in location, width and thickness. This results in
21 rejection of fewer dispensing devices for being out of specifications and also
22 provides dispensing devices having optimal surface characteristics and active
23 agent release profiles. The indexing or register means cooperates with the
24 banding means to align the unbanded dispensing device during the banding
25 operation.

26

27 The invention can best be understood with reference to the drawings.

28

29 FIG. 1 depicts, in side elevational view, one embodiment of the
30 unbanded dispensing device, which henceforth will be referred to as a
31 "blank". The blank is shown in prepared form prior to placement of the bands.

1 Blank 1 is shown in FIG. 1 to comprise a cylindrically shaped active agent
2 formulation matrix 12. The ends 14 and 16 of the matrix are pref rably
3 rounded and convex in shape in order to ensure ease of insertion into the
4 environment of use. Grooves 20, 22 and 24 are formed in and circumscribe
5 the exterior surface of the active agent formulation matrix 12. Multiple
6 grooves are illustrated. However, it will be appreciated that the blank may be
7 formed with only one groove or with more than one groove.

8

9 FIG. 2 shows blank 1 after the banding operation has been completed
10 and bands 30, 32, and 34 have been formed in grooves 20, 22, and 24,
11 respectively. That operation results in a delivery device that is suitable to be
12 placed in the fluid environment of use and operate as described in the '263
13 patent. Because the bands have been placed in the grooves and generally
14 will be configured to extend only to the outer surface of the blank, the outer
15 surface of the delivery device will be quite smooth. Optionally, however, the
16 completed device may be coated with a water-soluble film as described in the
17 '263 patent. The active agent formulation matrix 12 between bands 30, 32
18 and 34 and at its ends 14 and 16 will erode when the delivery device is
19 placed in the environment of use, thereby releasing active agent to the fluid
20 environment of use.

21

22 FIG. 3 shows a blank 1 having a single groove 44, shaped as a
23 concave surface, in the outer surface of active agent formulation matrix 42.
24 While a single groove is illustrated, more than one groove may be provided
25 depending on the number of bands that will be placed on the completed
26 delivery device.

27

28 FIG. 4 shows blank 1 after the banding operation has been completed
29 to form a completed delivery device. Groove 44 has been imprinted with
30 band 46, which, as illustrated, has to some extent assumed the concave
31 shape of groove 44. However, it is to be understood that band 46 may be

1 formed with additional material to fill groove 44 to provide an external surface
2 in the area of the groove that is level with the external surface of the active
3 agent formulation matrix 42 outside of the banded area. As has been
4 described previously, the banded dispensing device may be used in that
5 configuration, or it may be optionally over-coated with a water-soluble film as
6 described in the '263 patent. When placed in the environment of use, any
7 optional over-coated water soluble film will dissolve, and the external surface
8 of active agent matrix 42 not covered by band 46 will erode and release
9 active agent. Erosion will continue and the exposed ends will separate from
10 the banded portion of the device. Upon continued erosion, band 46 will
11 separate from any remaining active agent formulation matrix and will
12 thereafter be expelled from the fluid environment of use.

13

14 FIG. 5 shows another embodiment of a blank 1 of the invention having
15 a notched groove 54 formed with sloping sides 56. It is to be appreciated that
16 sides 56 could be formed at other angles to the longitudinal axis of the active
17 agent formulation matrix 52. For example, sides 56 could be at right angles
18 to the longitudinal axis. The particular choice of shape will be made by one
19 skilled in the art depending on application for which the dispensing device is
20 intended to be used.

21

22 FIG. 6 shows the blank of FIG. 5 after the banding operation has been
23 completed and a band 58 has been located in groove 54. The notched shape
24 facilitates the application of a uniform thickness of material forming band 58,
25 and may provide an external surface that is level with the surface of the active
26 agent formulation matrix 52. More than one groove 54 can be provided as
27 desired. The blank and delivery device can be utilized as described herein
28 and in accordance with the teachings of the '263 patent.

29

30 The number, size, and placement of the insoluble bands that are
31 applied onto the active agent formulation matrix may be varied to provide a

1 desired drug delivery profile, in conjunction with design of the active agent
2 formulation. For example, grooves of from about 0.1 mm to about 12 mm in
3 width, preferably between about 0.5 and 10 mm, and most preferably
4 between about 0.5 and 8 mm, may be formed into the blank, resulting in
5 bands of approximately that width on the active agent formulation matrix
6 surface. Typically, the grooves will be formed with a maximum depth of 0.1
7 mm to 3 mm, preferably 0.1 mm to 2 mm. However, for applications where
8 there is significant swelling of the polymer matrix of the tablet, the depth of the
9 groove may be greater to accommodate bands of increased thickness and
10 strength. Between about 1 and 10 bands may be used, but generally
11 between about 1 and 6 are affixed to the matrix. The bands may be placed
12 close together (i.e., within about 0.5 mm of each other) or may be placed at
13 opposite ends of the matrix (i.e., spaced about 8 to 12 mm apart).

14

15 The insoluble material may be any material that is nontoxic, biologically
16 inert, nonallergenic and nonirritating to body tissue, and that maintains its
17 physical and chemical integrity; that is, the bands do not erode or degrade in
18 the environment of use during the dispensing period. Insoluble materials from
19 which the bands may be prepared include, for example, polyethylene,
20 polystyrene, ethylene-vinyl acetate copolymers, polycaprolactone and Hytrel®
21 polyester elastomers (Du Pont). Additional banding materials include but are
22 not limited to polysaccharides, cellulosics, powdered cellulose,
23 microcrystalline cellulose, cellulose acetate, cellulose acetate pseudolatex
24 (such as described in U.S. Patent 5,024,842), cellulose acetate propionate,
25 cellulose acetate butyrate, ethyl cellulose, ethyl cellulose pseudolatex (such
26 as Surelease® as supplied by Colorcon, West Point, PA or Aquacoat™ as
27 supplied by FMC Corporation, Philadelphia, PA), nitrocellulose, polylactic
28 acid, poly- glycolic acid, polylactide glycolide copolymers, collagen,
29 polycaprolactone, polyvinyl alcohol, polyvinyl acetate, polyethylene
30 vinylacetate, polyethyl ne teraphthalate, polybutadi ne styrene,
31 polyisobutylene, polyisobutylene isoprene copolymer, polyvinyl chloride,

1 polyvinylidene chloride-vinyl chloride copolymer, copolymers of acrylic acid
2 and methacrylic acid esters, copolymers of methylmethacrylate and
3 ethylacrylate, latex of acrylate esters (such as Eudragit® supplied by
4 RöhmPharma, Darmstadt, Germany), polypropylene, copolymers of
5 propylene oxide and ethylene oxide, propylene oxide ethylene oxide block
6 copolymers, ethylenevinyl alcohol copolymer, polysulfone, ethylene
7 vinylalcohol copolymer, polyxylylenes, polyamides, natural and synthetic
8 waxes, paraffin, carnauba wax, petroleum wax, white or yellow bees wax,
9 castor wax, candelilla wax, rice bran wax, microcrystalline wax, stearyl
10 alcohol, cetyl alcohol, bleached shellac, esterified shellac, chitin, chitosan,
11 silicas, polyalkoxysilanes, polydimethyl siloxane, polyethylene glycol-silicone
12 elastomers, crosslinked gelatin, zein, electromagnetic irradiation crosslinked
13 acrylics, silicones, or polyesters, thermally crosslinked acrylics, silicones, or
14 polyesters, butadiene-styrene rubber, glycerol ester of partially dimerized
15 rosin, glycerol ester of partially hydrogenated wood rosin, glycerol ester of tall
16 oil rosin, glycerol ester of wood rosin, pentaerythritol ester of partially
17 hydrogenated wood rosin, pentaerythritol ester of wood rosin, natural or
18 synthetic terpene resin and blends of the above.

19
20 Preferred banding materials include copolymers of acrylic acid and
21 methacrylic acid esters, copolymers of methylmethacrylate and ethylacrylate,
22 and latex of acrylate esters. Preferred copolymers include poly (butyl
23 methacrylate, (2-dimethylaminoethyl)methacrylate, methyl methacrylate)
24 1:2:1, 150,000, sold under the trademark EUDRAGIT E; poly (ethyl acrylate,
25 methyl methacrylate) 2:1, 800,000, sold under the trademark EUDRAGIT NE
26 30 D; poly (methacrylic acid, methyl methacrylate) 1:1, 135,000, sold under
27 the trademark EUDRAGIT L; poly (methacrylic acid, ethyl acrylate) 1:1,
28 250,000, sold under the trademark EUDRAGIT L; poly (methacrylic acid,
29 methyl methacrylate) 1:2, 135,000, sold under the trademark EUDRAGIT S;
30 poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate
31 chloride) 1:2:0.2, 150,000, sold under the trademark EUDRAGIT RL; poly

1 (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate
2 chloride) 1:2:0.1, 150,000, sold as EUDRAGIT RS. In each case, the ratio
3 x:y:z indicates the molar proportions of the monomer units and the last
4 number is the number average molecular weight of the polymer. An
5 ethylacrylate methylmethacrylate 2:1 copolymer latex is especially preferred.

6

7 The banding materials often are also formulated with plasticizers, and
8 optionally with wetting agents, surfactants, opacifiers, colorants, flavorants,
9 taste-masking agents, and the like. Examples of typical plasticizers are as
10 follows: polyhydric alcohols, triacetin, polyethylene glycol, glycerol, propylene
11 glycol, acetate esters, glycerol triacetate, triethyl citrate, acetyl triethyl citrate,
12 glycerides, acetylated monoglycerides, oils, mineral oil, castor oil and the like.
13 Triacetin presently is a preferred plasticizer. The plasticizers may be blended
14 into the latex in amounts of 10-50 weight percent based on the weight of the
15 latex. Preferably, 20 - 40 weight percent of plasticizer, based on the weight of
16 the latex, may be utilized.

17

18 Tablets formed of the active agent formulation matrix are made by
19 standard granulation and tabletting methods. The tablet tooling however is of
20 particular design; it is made for use in the horizontal compression mode
21 ("HCT"), such as described, for example, in Remington's Pharmaceutical
22 Sciences, 14th Edition, pages 1660-1666. Tabletting design is described in
23 Pharmaceutical Dosage Forms: Tablets, Volume 2, Chapter 7, published by
24 Marcel Dekker, Inc. Tooling is designed with embossment to form one or
25 more grooves in the active agent formulation matrix as it is tabletted. The
26 HCT tablets are compressed such that at least one continuous groove is
27 embossed which lies in a plane perpendicular to the longitudinal axis of the
28 tablet and circumscribes a portion of the external surface of the tablet. Dies
29 and punches are fabricated with ridges that are located, shaped and sized to
30 form the grooves in the blanks as the active agent formulation matrix is
31 tabletted.

1 Fabrication of the completed delivery devices by banding the blanks of
2 the invention may take place on tablet or caplet banding systems and in
3 accordance with known banding processes as described generally below.

4

5 The grooved tablets formed in the tabletting operation are fed to a
6 banding machine (Tait or Shinonogi capsealer). The tablets roll on the
7 machine and when they reach the banding station, the printing wheel(s)
8 transfers coating material (e.g., ethylacrylate methylmethacrylate 2:1
9 copolymer latex) into the groove(s). Typically, one printing wheel
10 corresponding to each groove on the blank will be used. The width of the
11 wheels is smaller than the width of the grooves so that the printing surface of
12 the wheel rotates within the confines of the groove. The system continues to
13 rotate while the water of the latex is subsequently dried in a current of warm
14 air. The bands form within the grooves as the water is removed and the latex
15 coalesces. The system is optionally given a final film overcoat to complete
16 fabrication, as is described in the '263 patent. Bands of the resulting systems
17 have clean, straight borders, defined by the borders of the embossed grooves
18 and uniform thickness. Typically, the band edges will meet, or at least do not
19 extend above, the external surface of the active agent formulation matrix, thus
20 providing a smooth, continuous outer surface. While the invention is
21 described with the printing means comprising a printing wheel for application
22 of the banding material to the groove surface, it is understood that other
23 printing apparatus known to those skilled in the art, such as jet-droplet
24 printing, offset Gravure equipment, spray curtain printing, and the like, may be
25 used as well.

26

27 A schematic of a banding system useful in the practice of the invention
28 is illustrated in greater detail in FIGS. 7-10. As shown, the banding system
29 comprises a source of blanks, typically a vibratory or rotary feed hopper 61; a
30 transport mechanism to move blanks to the printing station, typically
31 comprising a rotating transport table 62, or alternatively a linear conveyer,

1 and a stationary table 63 upon which the blanks roll during processing; and
2 one or more banding stations 64 having a printing means, typically including a
3 source of banding material 65 and a printing wheel 66.

4

5 In the illustrated embodiment, the feed hopper 61 is positioned over
6 table 62 that is adapted to rotate horizontally over stationary table 63. Table
7 62 is formed with a plurality of slots or openings 67 that are positioned linearly
8 on respective radii of table 62 and are adapted to receive blanks from the
9 feed hopper. For ease of illustration, a single feed hopper that feeds a
10 plurality of slots 67 along a radius of table 62 is shown. Alternatively,
11 individual feed hoppers for each circumferential set of openings might be
12 used. Table 63 forms a stationary surface that supports the blanks as the
13 blanks are transported to banding station 64. Openings 68, shown in FIGS. 9
14 and 10, in stationary table 63 are sized to be slightly smaller than openings 67
15 so that the blanks continue to be supported at the banding station. Openings
16 68 are sized to accommodate the printing means so that banding material can
17 be applied to the grooves of the blank.

18

19 Located above table 62 is a drying apparatus, indicated generally as
20 69. Drying apparatus 69 may be of conventional design, including, for
21 example, a fan for forcing ambient air over a heater element to warm the air,
22 which is then directed with appropriate ducting to the area of table 62 in which
23 banded tablets are located. The banded tablets will continue to rotate
24 because of the rotation of table 62 over stationary table 63 and be dried as
25 they pass through the warm-air environment provided by the drying apparatus
26 69. While a single drying apparatus at a single drying station is shown, it will
27 be understood that multiple units may be used if necessary to complete the
28 drying of the banded tablets in a single cycle of rotation of table 62. In some
29 circumstances, particularly, where relatively thicker bands are deposited on
30 the blanks, a first drying apparatus may provide an initial amount of drying at
31 a lower temperature to prevent too rapid drying of the banding material, and

- 1 one or more additional drying apparatuses may provide additional drying
- 2 cycles at a higher temperature to complete final drying of the banded tablets.

3

4 Table 63 is formed with a second set of openings or a continuous slot
5 (not shown) extending along a radius of table 63 through which banded
6 tablets may be released from the slots 67 into a collection apparatus.

7

8 As table 62 rotates above the stationary surface of table 63, the blanks
9 rotate about their longitudinal axes as they are transported to the banding
10 station. Although only a single printing wheel 66 is shown for illustration
11 purposes, it is to be understood that a plurality of printing wheels may be
12 provided along a radius of table 62 under openings 67 so that each blank will
13 be appropriately banded as it reaches the banding station. In that manner,
14 each of the blanks positioned within openings 67 along a particular radius of
15 table 62 may be banded at the same time. In those instances where blanks
16 having a plurality of grooves are to be banded, it will usually be most efficient
17 to provide multiple printing wheels equal to the number of grooves at each
18 banding station so that each of the grooves may be banded simultaneously.
19 If it is desired, a similar banding station may be positioned at another set of
20 openings 67 in table 63 along other radii, thus providing the opportunity to
21 apply additional banding material to the banded blanks if thicker coatings or
22 coatings of different compositions are desired.

23

24 As shown in FIGS. 9 and 10, the grooves formed on the blanks of the
25 invention act as an indexing or register means to cooperate with the printing
26 means in the fabrication system and at the same time provide dispensing
27 devices having the desired release profile of active agent. With reference to
28 FIG. 9, blank 1 is shown at a location above a printing wheel 66. Groove 20
29 is indexed by and registers with banding wheel 66. The outer circumferential
30 surface of banding wheel 66 may be a generally planar surface 71 as shown
31 in FIG. 9, or it may be a concave surface 72 as shown in FIG. 10. The

1 concave surface is usually employed if thicker bands are required to obtain
2 the desired release profile of the active agent, since the concave surface
3 permits the application of a greater mass of banding material in a single
4 application than is possible with the flat surface. The printing surface of
5 printing wheel 66 may optionally be smooth or rough depending upon the
6 application intended. A rough surface can consist of a knurled surface, a
7 sandblasted or pebbled surface, or a matte finish. The purpose of the
8 roughened printing surface is to promote frictional contact to the blank as the
9 blank rotates over printing wheel 66 to enhance rotation with improved
10 traction. Another purpose of the roughened surface is to increase the
11 application rate of banding material 65 by increasing the amount of banding
12 material transferred from the band feed source per each rotation of the
13 printing wheel. The printing surface of the printing wheel can also be
14 configured with one or more channels to facilitate efficient transfer of the
15 banding material from the feed source to the blank. An end-on view of such a
16 printing wheel with a single channel 72 is illustrated in FIG. 10. The edges 73
17 and 74 forming the channel may be smooth or roughed as discussed
18 previously with respect to the planar surface of printing wheel 66. As printing
19 wheel 66 rotates through the banding material, it picks up banding material on
20 its circumferential surface and deposits it onto the surface of groove 20. The
21 rate of rotation of table 62 is adjusted to provide a residence time for the
22 blanks at the banding station that is adequate to allow for application of the
23 desired amount of banding material. Typically, table 62 will rotate in a range
24 of 0.25 to 2.1 revolutions per minute (rpm) and printing wheel 66 will rotate in
25 a range of 15 to 120 rpm. For most typical applications, table 62 preferably
26 rotates between 0.5 and 0.75 rpm, most preferably between 0.6 and 0.7 rpm,
27 and printing wheel 66 preferably rotates between 30 and 60 rpm, most
28 preferably between 40-50 rpm.

29

30 The groov s in the blanks additionally act as templates for the
31 formation of bands on the dosage forms, thus facilitating control of the width,

1 depth, location and edge characteristics of the bands. Also, banded dosage
2 forms having a smooth, outer surface can be produced with or without coating
3 of an overlayer on the banded tablet.

4

5 Fabrication of expandable dosage forms, for example, those intended
6 for gastric retention, follows a similar procedure. In this case, the groove
7 which circumscribes the tablet may be either shallow or deep. However, if the
8 dosage form is intended to expand significantly from uptake of fluid (e.g.
9 100% to 500% of its dry volume), deeper grooves usually will be employed.
10 In the deep-groove configuration, the shape of the groove can be in the form
11 of a notch or a saddle point (Figures 3-6). The diameter of the tablet at these
12 deep-grooved areas is smaller than the tablet diameter overall. Therefore,
13 when this core is banded at a fixed wheel rotation speed and fixed dwell time,
14 a thicker band can form within the groove than would be formed without the
15 groove. Thick, robust rings are needed when the gastric retention system is
16 in operation to withstand the pressure generated by high-swelling fibers and
17 hydrogels of the core as the system enlarges to dimensions larger than the
18 pylorus. Typically, deep-grooved rings will have a maximum depth of from
19 about 0.5 mm to about 3 mm, although it is understood that the thickness may
20 be less or greater as selected by one skilled in the art for the particular
21 application at hand.

22

23 FIG. 11 illustrates a typical blank 1 formed with a groove 20 from
24 horizontal compression of the bulk active agent formulation. In contrast to
25 conventional gelatin capsules that have a smooth outer surface and are
26 generally of circular cross-section, a horizontally compressed blank may have
27 a number of surfaces, such as the land area designated 75 and surfaces 76
28 and 77, that impart some non-circular irregularity to the cross-section of the
29 tablet. Application of the banding material according to the process of the
30 present invention typically will cover those surfaces with banding material to
31 provide a smooth surface after banding. To the extent that the land area

- 1 outside of the groove is not covered by banding material, the banded tablet
- 2 may be overcoated as described previously to provide for a smooth, outer
- 3 surface.

4

5 The active agent of the active agent formulation may be in liquid, solid
6 or semisolid form. The active agent formulation may contain additional
7 materials and may be designed in a multitude of ways to provide a specific
8 drug delivery profile. One embodiment comprises a formulation that contains
9 a biologically acceptable hydrophilic polymer which is capable of slow
10 dispersion in the environmental fluid. In another embodiment, the formulation
11 may contain a hydrophilic polymer and a surfactant so that the formulation is
12 susceptible to erosion in the environment. In still another embodiment, the
13 formulation may include a solid surfactant so that the formulation is
14 susceptible to erosion in the environment. In still another embodiment, the
15 formulation may include a solid surfactant and provide drug delivery in a finely
16 dispersed form. In yet a further embodiment, the formulation may include
17 coated microspheres of an active agent and an adjuvant. The active agent
18 and adjuvant can be delivered simultaneously from the microspheres either
19 by diffusion or by osmosis. Suitable materials useful as active agent carriers
20 and excipients are known in the art and are disclosed in U.S. Patent Nos.
21 4,595,583 and 4,874,388, for example.

22

23 The terms "active agent" and "drug" are used interchangeably herein
24 and refer to an agent, drug, compound, composition of matter or mixture
25 thereof which provides some pharmacologic, often beneficial, effect. This
26 includes pesticides, herbicides, germicides, biocides, algicides, rodenticides,
27 fungicides, insecticides, antioxidants, plant growth promoters, plant growth
28 inhibitors, preservatives, antipreservatives, disinfectants, sterilization agents,
29 catalysts, chemical reactants, fermentation agents, foods, food supplements,
30 nutrients, cosmetics, drugs, vitamins, sex sterilants, fertility inhibitors, f utility
31 promoters, microorganism attenuators and other agents that benefit the

1 environment of use. As used herein, the terms further include any
2 physiologically or pharmacologically active substance that produces a
3 localized or systemic effect or effects in animals, including warm blooded
4 mammals, humans and primates; avians; domestic household or farm
5 animals such as cats, dogs, sheep, goats, cattle, horses and pigs; laboratory
6 animals such as mice, rats and guinea pigs; fish; reptiles; zoo and wild
7 animals; and the like. The active drug that can be delivered includes
8 inorganic and organic compounds, including, without limitation, drugs which
9 act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the
10 skeletal muscles, the cardiovascular system, smooth muscles, the blood
11 circulatory system, synoptic sites, neuroeffector junctional sites, endocrine
12 and hormone systems, the immune system, the reproductive system, the
13 skeletal system, autacoid systems, the alimentary and excretory systems, the
14 histamine system and the central nervous system. Suitable agents may be
15 selected from, for example, proteins, enzymes, hormones, polynucleotides,
16 nucleoproteins, polysaccharides, glycoproteins, lipoproteins, polypeptides,
17 steroids, hypnotics and sedatives, psychic energizers, tranquilizers,
18 anticonvulsants, muscle relaxants, antiparkinson agents, analgesics,
19 antiepileptics, antibiotics, anti-inflammatories, local anesthetics, muscle
20 contractants, antimicrobials, antivirals, antimalarials, hormonal agents
21 including contraceptives, sympathomimetics, polypeptides and proteins
22 capable of eliciting physiological effects, diuretics, lipid regulating agents,
23 antiandrogenic agents, antiparasitics, neoplastics, antineoplastics,
24 hypoglycemics, nutrional agents and supplements, growth supplements, fats,
25 ophthalmics, antienteritis agents, electrolytes and diagnostic agents.

26
27 Examples of beneficial agents useful in this invention include
28 prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, mecamylamine
29 hydrochloride, procainamide hydrochloride, amphetamine sulfate,
30 methamphetamine hydrochloride, benzphetamine hydrochloride,
31 isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride,

- 1 methacholine chloride, pilocarpine hydrochloride, atropine sulfate,
- 2 scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin
- 3 hydrochloride, methylphenidate hydrochloride, theophylline choline,
- 4 cephalixin hydrochloride, diphenidol, meclizine hydrochloride,
- 5 prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate,
- 6 anisindione, diphenadione erythrityl tetranitrate, digoxin, isofluorophate,
- 7 acetazolamide, methazolamide, bendroflumethiazide, phenytoin, minocycline,
- 8 acyclovir, ganciclovir, fenoxyadine, chlorpropamide, tolazamide,
- 9 chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin,
- 10 fexofenadine, methotrexate, acetyl sulfisoxazole, hydrocortisone,
- 11 hydrocorticosterone acetate, cortisone acetate, dexamethasone and its
- 12 derivatives such as betamethasone, triamcinolone, methyltestosterone, 17- β -
- 13 estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17-
- 14 β -hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel,
- 15 norethindrone, norethisterone, norethiederone, progesterone, norgesterone,
- 16 norethynodrel, aspirin, acetaminophen, indomethacin, naproxen, fenoprofen,
- 17 sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol,
- 18 atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa,
- 19 chlorpromazine, methyldopa, dihydroxyphenylalanine, calcium gluconate,
- 20 ketoprofen, ibuprofen, cephalixin, erythromycin, haloperidol, zomepirac,
- 21 ferrous lactate, vincamine, phenoxybenzamine, diltiazem, milrinone,
- 22 captopril, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen,
- 23 fenbufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuninal,
- 24 nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine,
- 25 tiapamil, gallopamil, amlodipine, mioflazine, lisinopril, enalapril, captopril,
- 26 ramipril, enalaprilat, famotidine, nizatidine, sucralfate, etintidine, tetratolol,
- 27 minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further
- 28 examples are proteins and peptides which include, but are not limited to,
- 29 insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and
- 30 pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic
- 31 hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin

1 releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin,
2 vasopressin, prolactin, somatostatin, lypressin, pancreazymin, luteinizing
3 hormone, LHRH, interferons, interferins, growth hormones such as human
4 growth hormone, bovine growth hormone and porcine growth hormone,
5 fertility inhibitors such as the prostaglandins, fertility promoters, growth
6 factors, and human pancreas hormone releasing factor.

7

8 It is to be understood that more than one active agent may be
9 incorporated into the active agent formulation in a device of this invention,
10 and that the use of the term "agent" or "drug" in no way excludes the use of
11 two or more such agents or drugs.

12

13 The agents can be in various forms, such as uncharged molecules,
14 components of molecular complexes or nonirritating, pharmacologically
15 acceptable salts. Also, simple derivatives of the agents (such as ethers,
16 esters, amides, etc) which are easily hydrolyzed by body pH, enzymes, etc,
17 can be employed.

18

19 The amount of active agent employed in the delivery device will be that
20 amount necessary to deliver a therapeutically effective amount of the agent to
21 achieve the desired result at the site of delivery. In practice, this will vary
22 widely depending upon the particular agent, the site of delivery, the severity of
23 the condition, and the desired therapeutic effect. Thus, it is not practical to
24 define a particular range for the therapeutically effective amount of active
25 agent incorporated into the device.

26

27 The hydrophilic polymeric material useful herein may comprise,
28 polysaccharides, methyl cellulose, sodium or calcium carboxymethyl
29 cellulose, nitrocellulose, carboxymethyl cellulose and other cellulose ethers,
30 and polyethylene oxides (e.g., Polyox®, Union Carbide). Other materials
31 useful as the hydrophilic polymeric material include but are not limited to

1 hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose,
2 hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl ethyl cellulose,
3 ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose
4 propionate, cellulose fibers, gelatin, collagen, starch, maltodextrin, pullulan,
5 polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid
6 esters, polyacrylamide, polyacrylic acid, sodium and potassium salts of
7 polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (Eudragit™)
8 or other acrylic acid derivatives, sorbitan esters, natural gums, lecithins,
9 pectin, alginates, ammonia alginate, sodium or potassium alginate, calcium
10 alginate, propylene glycol alginate, potassium alginate, agar, gum arabic,
11 gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti,
12 guar gum, xanthan gum, scleroglucan, and blends of the above.

13

14 The pharmaceutically acceptable carrier useful herein may comprise
15 more than one ingredient, such as, for example, a buffer, a viscosity
16 regulating vehicle, a surfactant, a dye, a permeation enhancer, a proteinase
17 inhibitor, or other formulation ingredients and additives, as are known in the
18 art.

19

20 The rate of release of the active agent from the active agent dosage
21 forms is predominantly controlled by erosion of the aqueous gel formed by
22 contacting the matrix with the fluid environment of use.

23

24 The rate of active agent released from a cylindrical dosage form
25 without bands versus time will continuously decrease with time. As drug is
26 released from an unbanded capsule, the diameter of the cylinder as well as
27 the area of erosion decreases. In contrast, as the polymeric core of the
28 banded cylinder of this invention shrinks, new surface area is created and
29 exposed to the environment of use as described in greater detail in the '263
30 patent. As a result, the amount of active agent released over time may
31 remain constant or may increase with time depending on the rate of the new

1 surface area being generated. By arrangement of the number, size and
2 location of bands on the dosage form, the total new surface area created by
3 erosion can be predicted and the desired release profile can be achieved.

4

5 The bands may be placed onto the surface of the matrix such that, as
6 the matrix erodes, the bands become loose and drop off the matrix. These
7 bands are easily excreted from the gastrointestinal tract. As the number of
8 bands remaining on the surface of the matrix decreases, more matrix surface
9 area will be exposed. The matrix will therefore erode in a fashion that
10 approaches zero order rate.

11

12 In order to prepare a device of the present invention, the active agent
13 formulation is first prepared and formed into a blank of the desired size and
14 shape and having the desired number of grooves with the desired groove
15 shape. The matrix in its initial prepared form is about the size and
16 dimensions of a size "5" to size "000" hard gelatin capsule. The cross-
17 sectional shape of the matrix may be circular or may be oval or other shapes
18 that are able to be manipulated by the banding system, indexed by means of
19 the grooves acting as registers and printed. Generally, shapes that are easily
20 rotated by the printing wheel of the systems described herein, e.g., circular
21 and oval, will be most preferred.

22

23 The following examples are illustrative of the present invention. They
24 are not to be construed as limiting the scope of the invention. Variations and
25 equivalents of these examples will be apparent to those skilled in the art in
26 light of the present disclosure, the drawings and the claims herein.

27

28 EXAMPLE 1

29

30 A delivery device according to the present invention is prepared as
31 follows. 580 grams of the analgesic drug, ibuprofen, 250 grams of

1 hydroxypropyl methylcellulose having a number average molecular weight of
2 9,200 grams per mole, and 150 grams of hydroxypropyl methylcellulose
3 having a molecular weight of 242,000 grams per mole, is passed through a
4 screen having a mesh size of 40 wires per inch. The cellulose each have an
5 average hydroxyl content of 8 weight percent and an average methoxyl
6 content of 22 weight percent. The resulting sized powders are tumble mixed.
7 Anhydrous ethyl alcohol is added slowly to the mixed powders with stirring
8 until a dough consistency is produced. The damp mass is then extruded
9 through a 20 mesh screen and air dried overnight. The resulting dried
10 material is re-screened through a 20 mesh screen to form the final granules.
11 2 grams of the tabletting lubricant, magnesium stearate, which has been
12 sized through an 80 mesh screen, is then tumbled into the granules.

13

14 690 mg of the resulting granulation is placed in a die cavity formed with
15 three, uniformly spaced convex ridges, each having a semi-circular cross-
16 sectional shape and a height of 0.7 mm. The inside dimensions of the die,
17 not including the ridged areas, are 15 mm by 9 mm. The granulation is
18 horizontally compressed with deep concave punch tooling using a punch
19 formed with ridges on its interior surface that correspond to the ridges in the
20 die to form complementary groove when the compression operation is
21 completed. Compression takes place at a pressure head of 2 tons. This
22 forms a longitudinal blank having an overall length, including the rounded
23 ends, of 15 mm and a concave groove with a depth of 0.7 mm. The
24 cylindrical body of the blank, from tablet land to tablet land, spans a distance
25 of 9 mm. Each blank contains a unit dose of drug of 400 mg. The capsules
26 are fed into a Tait Capsealer Machine (Tait Design and Machine Co.,
27 Manheim, PA), modified as described herein, where the rotating printing
28 wheels engage the grooves and align the blank for the printing operation.
29 Three bands are printed onto each capsule. The material forming the bands
30 is a mixture of 50 wt% ethylcellulose dispersion (Surelease®, Colorcon, West
31 Point, PA) and 50 wt% ethyl acrylate methylmethacrylate (Eudragit® NE 30D,

1 RöhmPharma, Weiterstadt, Germany). The bands are applied as an aqueous
2 dispersion and the excess water is driven off in a current of warm air. The
3 diameter of the bands is 2 millimeters. The finished dosage form has a
4 smooth outer surface and delivers ibuprofen over a prolonged period of time.

5

6 Drug release studies are performed by placing the dosage forms in a
7 slotted basket. The inside diameter of the basket is 14 mm and the length is
8 50 mm. The basket is attached to a reciprocating motor. The basket is then
9 immersed in 50 ml of simulated intestinal fluid at 37°C, and shaken vertically
10 in the media with a amplitude of 3.8 cm and a frequency of 99-101 cycles per
11 minute. After 1 hour of shaking, the basket is transferred to a fresh 50 ml
12 volume of the test media. This procedure is continued, hour by hour, for nine
13 hours. The systems then are allowed to release continuously for another 13
14 hours to complete a 24 hour test duration. The release receptor solutions are
15 then analyzed for drug content by ultraviolet spectroscopy. The release rate
16 as a function of time and cumulative release as a function of time are
17 computed. The delivery devices of the invention release active agent over a
18 prolonged period of time.

19

20 EXAMPLE 2

21

22 A blank with the ibuprofen matrix formulation described in Example 1 is
23 formed with one notched groove having sloping side wall at an angle of 30
24 degrees with the longitudinal axis of the tablet and banded with one band.
25 The resulting dosage form has a substantially smooth outer surface, with the
26 edges and thickness of the bands being substantially uniform. The dosage
27 form delivers ibuprofen over a prolonged period.

28

29

30

31

1

EXAMPLE 3

2

3 A fast-release drug granulation is prepared as follows; 870 grams of
4 ibuprofen, 100 grams of hydroxypropyl cellulose having a hydroxypropoxyl
5 content of 11 weight percent, and 10 grams of hydroxypropyl methyl cellulose
6 having a hydroxypropoxyl content of 8 weight percent and a methoxy content
7 of 22 weight percent and having a number average molecular weight of 9,200
8 grams per mole, are screened through a 40 mesh sieve. The sized powders
9 are mixed and anhydrous ethanol is added with stirring until a uniform, damp
10 mass is produced. The mixture is extruded through a 20 mesh sieve. The
11 elongated granules produced are air dried. The dried granules are re-
12 screened through a 20 mesh sieve. 20 Grams of stearic acid which has been
13 passed through an 80 mesh sieve are tumble mixed into the granules for 3
14 minutes.

15

16 690 mg of the granulation of Example 1 is filled into a die cavity having
17 two semicircular ridges with sides at an angle of 30 degrees with the
18 longitudinal axis of the die and an inside diameter in an area not including the
19 ridges of 6 mm and horizontally lightly compressed with deep concave punch
20 tooling. The upper punch is removed and 230 mg of the fast-release
21 granulation is placed on the lightly compressed core. A second upper punch,
22 formed with two ridges that cooperate with the ridges in the die to create the
23 two grooves in the blank, is placed in the die cavity and a 2 ton compression
24 force is applied, thereby forming a two-layered tablet. Two rings are printed
25 onto the dosage form according to the procedures herein.

26

27 An abrasion resistant, protective coating is applied to the banded, two-
28 layered tablet as follows. A coating solution is prepared by dissolving 63
29 grams of hydroxypropyl methylcellulose having a hydroxypropoxyl content of
30 10 weight percent and a methoxy content of 29 weight percent with a number
31 average molecular weight of 11,900 grams per mole, and 7 grams of

1 polyethylene glycol having a molecular weight of 3,350 grams per mole, in
2 930 grams of water. The banded dosage form is then placed in a pan coating
3 machine. The coating solution is sprayed onto the banded tablet in a current
4 of warmed air until 40 mg of film are deposited on each tablet.

5

6 The resulting two-layer, film coated system releases a portion of
7 ibuprofen rapidly and a portion of ibuprofen over a prolonged period.

8

9 The above description has been given for ease of understanding only.
10 No unnecessary limitations should be understood therefrom, as modifications
11 will be obvious to those skilled in the art.

12

What is claimed is:

1. A method of preparing an active agent dosage form for the prolonged delivery of the active agent, comprising:
 - forming a blank from an active agent formulation matrix so that the blank has a groove circumscribing a portion of the external surface of the blank; and
 - depositing insoluble material in the groove.
2. The method of claim 1, wherein said forming step comprises:
 - compressing the active agent formulation matrix; and
 - embossing the groove in the active agent formulation matrix so that it lies in a plane perpendicular to the longitudinal axis of the blank.
3. The method of claim 1, wherein said depositing step comprises:
 - using printing means to transfer insoluble material into the groove.
4. The method of claim 3, wherein the printing means comprises a rotatable wheel.
5. The method of claim 4, wherein the wheel has a substantially planar outer circumferential surface.
6. The method of claim 4, wherein the wheel has a concave outer circumferential surface.
7. The method of claim 1, wherein said depositing step is carried out so that the insoluble material does not extend above the external surface of the blank.
8. The method of claim 1, further comprising:
 - coating the blank with a water-soluble film.
9. A method for fabricating an active agent dosage form for the prolonged delivery of the active agent, comprising:
 - providing a blank, the blank comprising an active agent formulation matrix having a groove circumscribing a portion of the external surface of the blank;
 - orienting the blank with respect to a forming means for forming a band in the groove; and
 - forming the band in the groove using the forming means.
10. The method of claim 9, wherein said orienting step comprises:

registering the forming means with the groove.

11. The method of claim 10, wherein said registering step is carried out using a rotatable wheel.
12. The method of claim 9, wherein said forming step comprises:
using printing means to transfer insoluble material into the groove.
13. The method of claim 12, wherein the printing means comprises a rotatable wheel.
14. The method of claim 13, wherein the wheel has a substantially planar outer circumferential surface.
15. The method of claim 13, wherein the wheel has a concave outer circumferential surface.
16. The method of claim 9, wherein said forming step is carried out so that the band does not extend above the external surface of the blank.
17. The method of claim 9, further comprising:
coating the blank with a water-soluble film.
18. The method of claim 9, further comprising:
transporting the blank from a source of blanks to the forming means.
19. An active agent dosage form for the prolonged delivery of an active agent formulation to a fluid environment of use, comprising:
an active agent formulation matrix having a groove circumscribing a portion of the external surface thereof; and
an insoluble band disposed in said groove.
20. The active agent dosage form of claim 19, wherein said groove has a notch shape.
21. The active agent dosage form of claim 19, wherein said groove has a concave shape.
22. The active agent dosage form of claim 19, wherein the depth of said groove is between about 0.1mm and about 3mm.
23. The active agent dosage form of claim 19, wherein the width of said groove is between about 0.5mm and 10mm.
24. The active agent dosage form of claim 19, further comprising:

a water-soluble film coating.

25. The active agent dosage form of claim 19, wherein the dosage form comprises a plurality of grooves, each of said grooves circumscribing a portion of the external surface of the active agent formulation matrix.

26. The active agent dosage form of claim 25, wherein the dosage form comprises an insoluble band disposed in each of said grooves.

27. The active agent dosage form of claim 19, wherein said insoluble band comprises a latex of acrylate polymers.

28. The active agent dosage form of claim 27, wherein said acrylate polymers comprise copolymers of ethylacrylate and methylmethacrylate.

29. The active agent dosage form of claim 28, wherein said copolymers comprise an ethylacrylate methylmethacrylate 2:1 copolymer latex.

30. A blank for formation of a pharmaceutical dosage form for controlled delivery of an active agent, comprising:

an active agent formulation matrix having a groove circumscribing a portion of the external surface of said matrix.

31. The blank of claim 30, wherein said groove has a notch shape.

32. The blank of claim 30, wherein said groove has a concave shape.

33. The blank of claim 30, wherein the depth of said groove is between about 0.1mm and about 3mm.

34. The blank of claim 30, wherein the width of said groove is between about 0.5mm and 10mm.

35. The blank of claim 30, wherein said active agent formulation matrix has a cylindrical shape, the ends of which are rounded and convex.

36. A system for fabricating an active agent dosage form for the prolonged delivery of the active agent, comprising:

forming means for forming a band in a groove circumscribed on the external surface of a blank; and

orienting means for orienting, by way of the groove, the blank with respect to said forming means.

37. The system of claim 36, wherein said orienting means comprises means registering with the groove on the blank.

38. The system of claim 37, wherein said means registering with the groove comprises a rotatable wheel.

39. The system of claim 36, wherein said forming means comprises:

a source of material for the band; and
a printing wheel.

40. A system for fabricating an active agent dosage form for the prolonged delivery of the active agent, comprising:

a source of blanks, each of said blanks having a groove circumscribing a portion of the external surface of the blank; and

a banding station that forms a band of insoluble material in the groove.

41. The system of claim 40, wherein said banding station comprises:

a printing means.

42. The system of claim 41, wherein said printing means comprises:

a source of insoluble material; and
a printing wheel.

43. The system of claim 42, wherein said printing wheel has a substantially planar outer circumferential surface.

44. The system of claim 42, wherein said printing wheel has a concave outer circumferential surface.

45. The system of claim 40, further comprising:

a transport mechanism that transports the blanks from said source to said banding station.

46. The system of claim 45, wherein said transport mechanism comprises:
 - a stationary table; and
 - a rotating transport table adapted to rotate over said stationary table.
47. The system of claim 46, wherein said rotating transport table defines a plurality of openings positioned linearly on respective radii, said openings adapted to receive blanks from said source.
48. The system of claim 40, further comprising:
 - a drying apparatus configured to dry the band.

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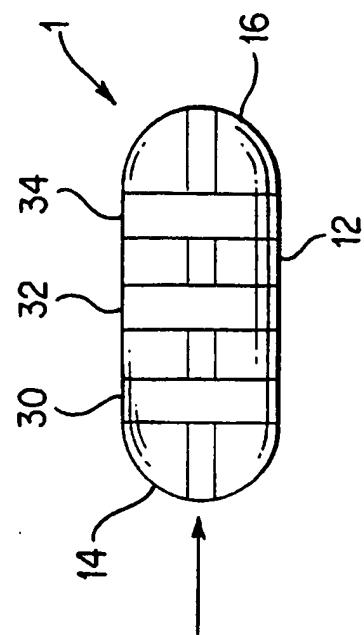


FIG. 2

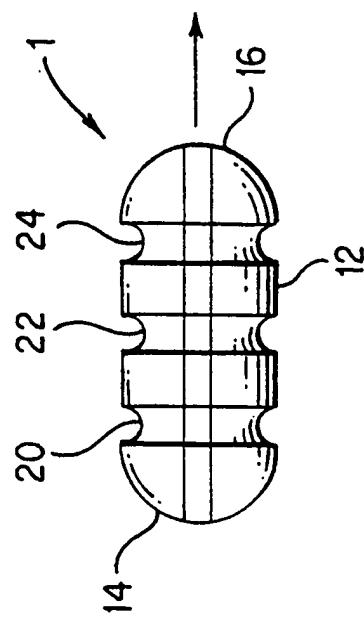


FIG. 1

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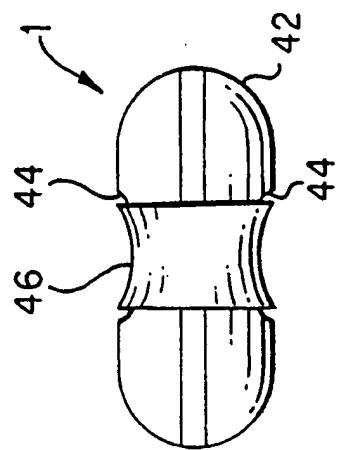


FIG. 3

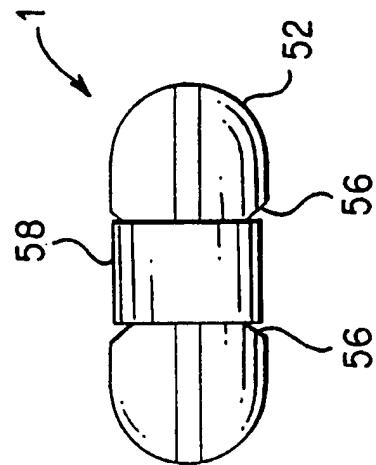


FIG. 4

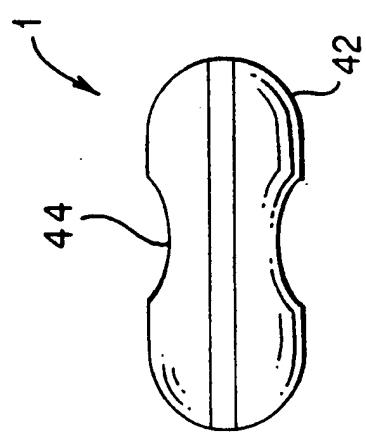


FIG. 5

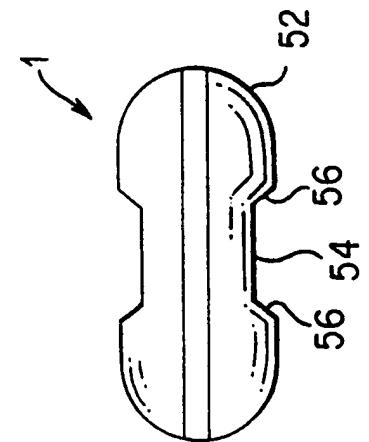


FIG. 6

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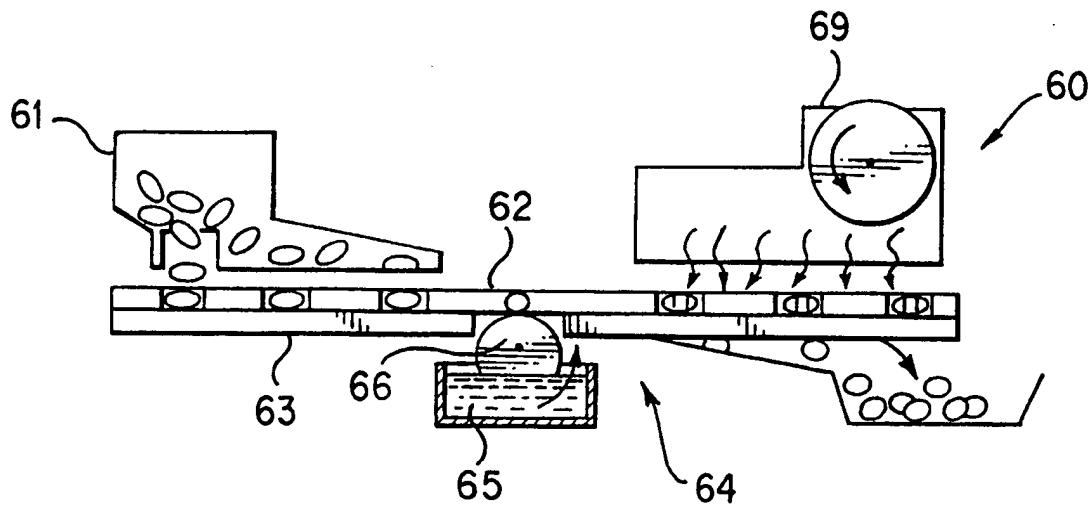


FIG. 7

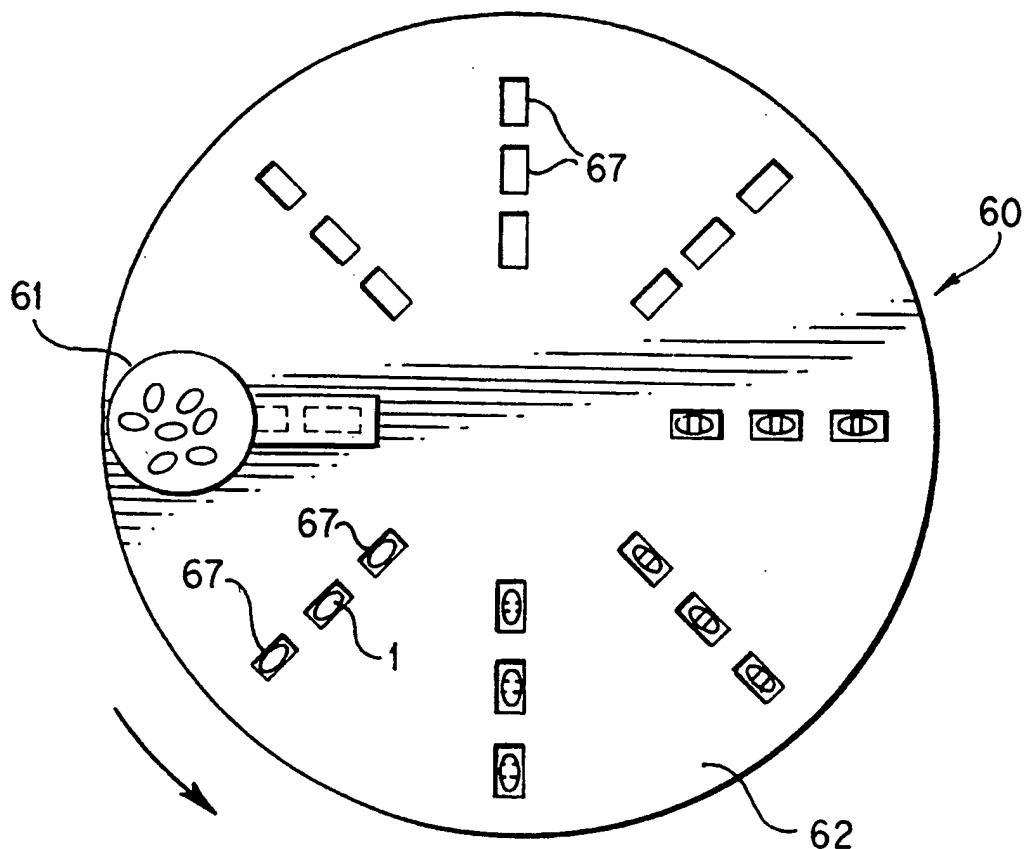


FIG. 8

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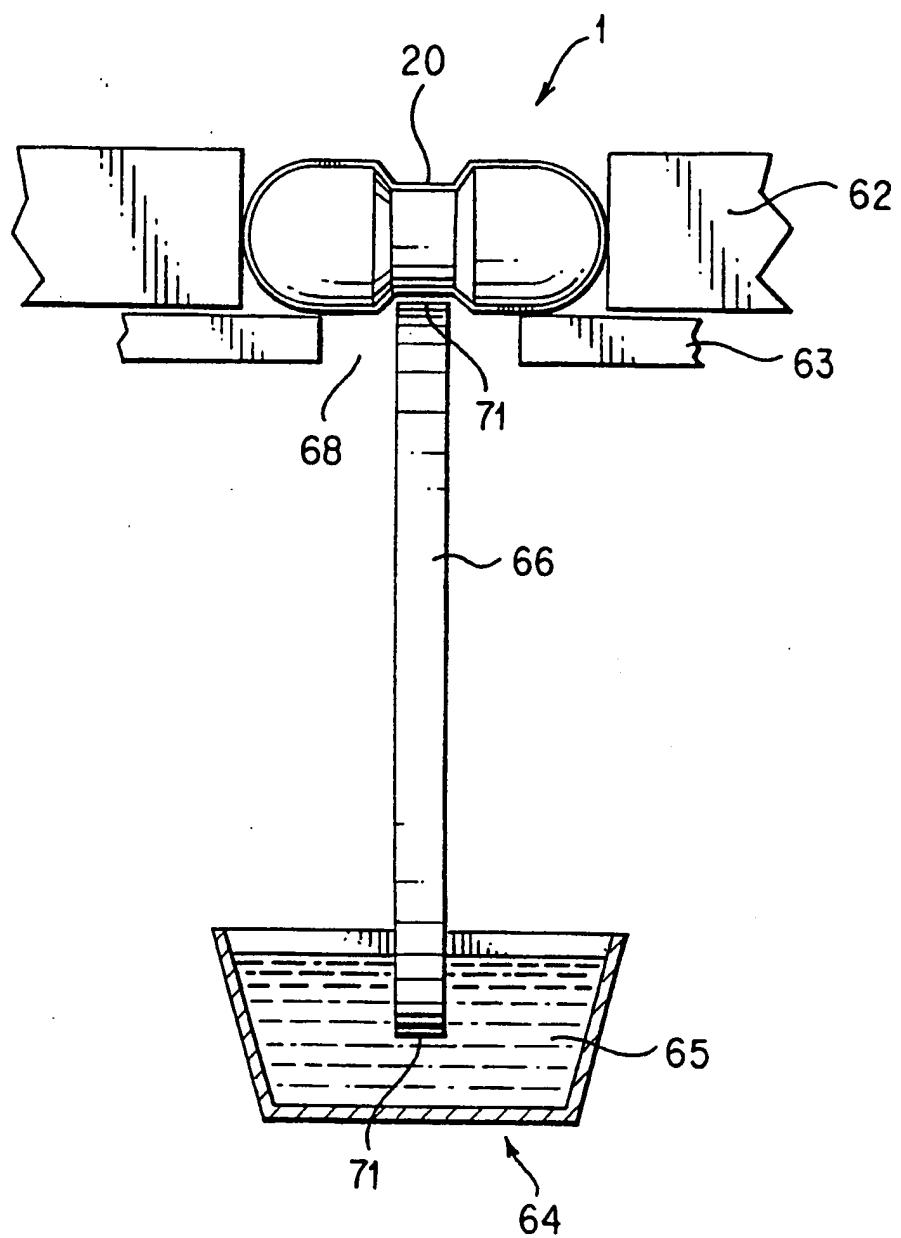


FIG. 9

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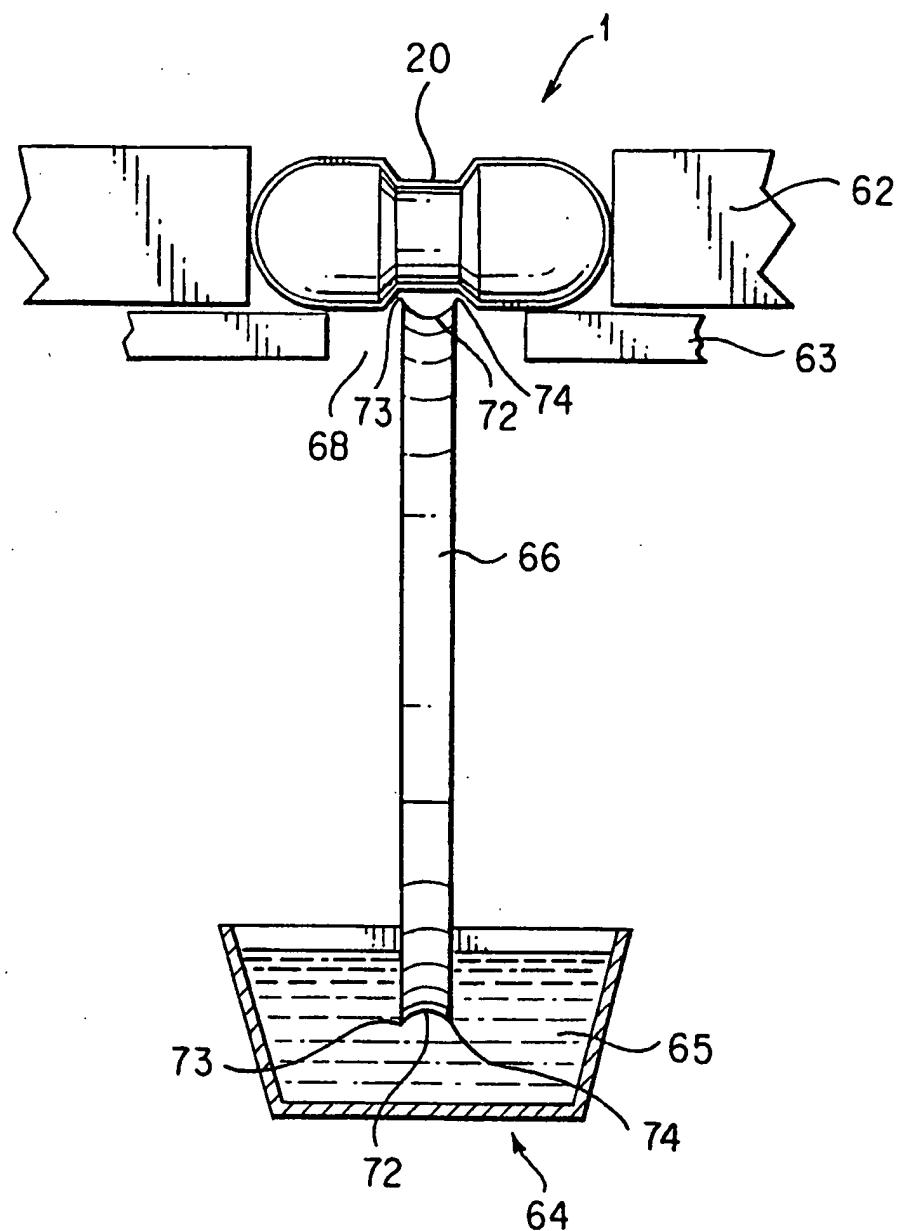


FIG. 10

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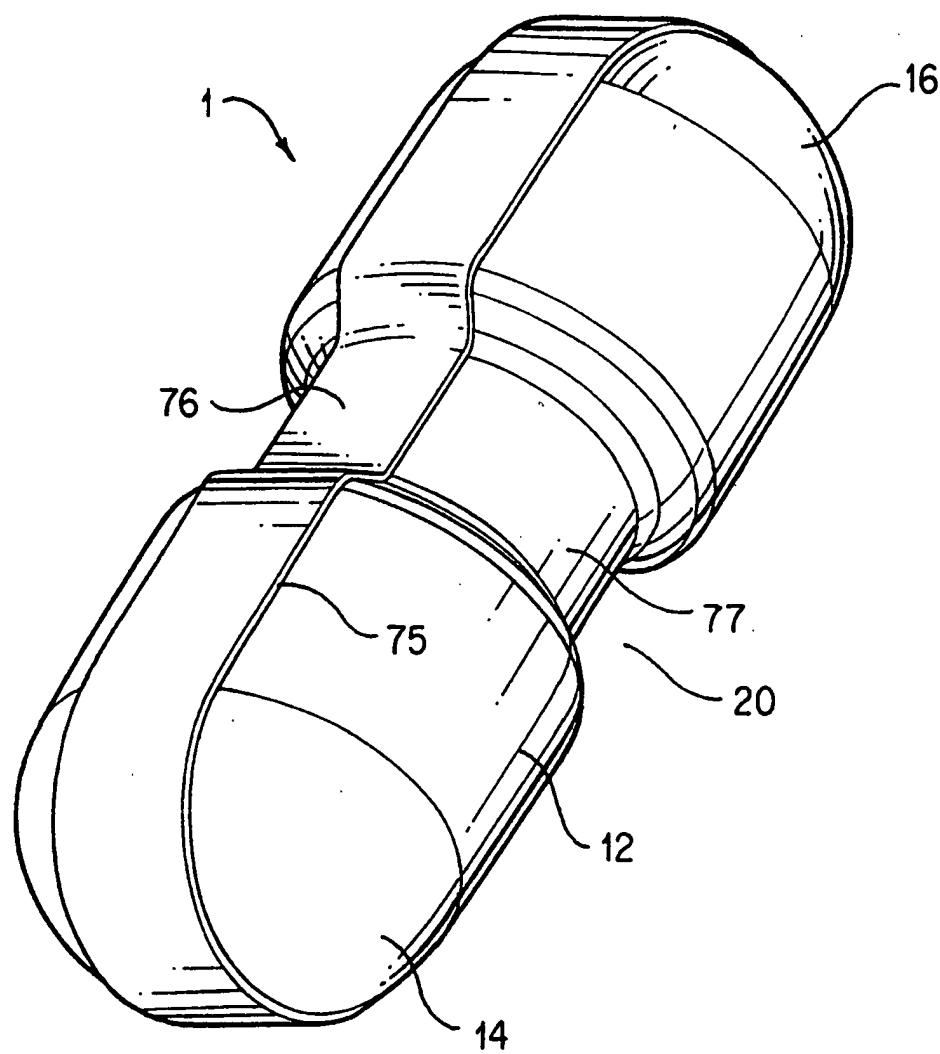


FIG.11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/09575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 088 556 A (SUMITOMO CHEMICAL CO) 14 September 1983 (1983-09-14)</p> <p>page 2, line 17 - page 3, line 12 page 3, line 27 - page 4, line 2 page 4, line 13 - line 25 claims; examples</p> <p>---</p> <p>DE 43 41 548 A (BRENNER FRANK) 8 June 1995 (1995-06-08) column 1, line 35 - line 47 column 1, line 59 - column 2, line 5 claims 1,5,6; figures 1-3</p> <p>---</p> <p>-/-</p>	<p>1,7,8, 19, 22-26, 30,33, 34,40</p> <p>30-32,35</p>
X		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

2 August 1999

Date of mailing of the international search report

10/08/1999

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Authorized officer

Epskamp, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/09575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 052 376 A (ZELLERS EDGAR G) 25 August 1936 (1936-08-25) page 2, column 1, line 9 - line 14 figure 6 ---	30,31,35
X	US 2 962 851 A (HALL VICTOR C) 6 December 1960 (1960-12-06)	36-39
A	column 1, line 15 - line 19 column 1, line 72 - column 2, line 5 claims; figures 1,4,17-21,27,35-38 ---	40-48
X	EP 0 403 214 A (NIPPON ELANCO) 19 December 1990 (1990-12-19)	36-39
A	column 2, line 54 - column 3, line 2 claims; figures 1,2,9-11 ---	40-48
A	US 5 534 263 A (WONG PATRICK S-L ET AL) 9 July 1996 (1996-07-09) cited in the application claims; figures; examples 1,4-6 ----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/US 99/09575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0088556	A 14-09-1983	JP 58152813 A CA 1222696 A DK 111783 A, B, US 5002775 A	10-09-1983 09-06-1987 09-09-1983 26-03-1991
DE 4341548	A 08-06-1995	NONE	
US 2052376	A 25-08-1936	NONE	
US 2962851	A 06-12-1960	NONE	
EP 0403214	A 19-12-1990	JP 2675142 B JP 3012160 A CA 2018531 A, C DE 69021134 D DE 69021134 T ES 2075157 T US 5094184 A	12-11-1997 21-01-1991 12-12-1990 31-08-1995 21-12-1995 01-10-1995 10-03-1992
US 5534263	A 09-07-1996	AU 703681 B AU 5022696 A CA 2207098 A CN 1175901 A EP 0810856 A FI 973452 A JP 11500728 T NO 973840 A NZ 303809 A WO 9625922 A US 5667804 A	01-04-1999 11-09-1996 29-08-1996 11-03-1998 10-12-1997 22-08-1997 19-01-1999 22-10-1997 29-04-1999 29-08-1996 16-09-1997